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The effect of ICAD-S on the formation and intracellular distribution of a nucleolytically active caspase-activated DNase

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Abstract

We show here that co-expression of murine CAD with either ICAD-L or ICAD-S in Escherichia coli as well as mammalian cells leads to a functional DFF complex, which after caspase-3 activation releases a nucleolytically active DNase. The chaperone activity of ICAD-S is between one and two orders of magnitude less effective than that of ICAD-L, as deduced from cleavage experiments with different activated recombinant DFF complexes produced in Ecoli. With nucleolytically active EGFP fusion proteins of CAD it is demonstrated that co-expression of ICAD-S, which lacks the C-terminal domain of ICAD-L, including the NLS, leads to a homogeneous intracellular distribution of the DNase in transfected cells, whereas co-expression of human or murine ICAD-L variants lacking the NLS leads to exclusion of EGFP-CAD from the nuclei in ~50% of cells. These results attribute a particular importance of the NLS in the long isoform of the inhibitor of CAD for nuclear accumulation of the DFF complex in living cells. It is concluded that ICAD-L and ICAD-S in vivo might function as tissue-specific modulators in the regulation of apoptotic DNA degradation by controlling not only the enzymatic activity but also the amount of CAD available in the nuclei of mammalian cells.